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(54) Title: BLOCK COPOLYMER MICELLE COMPOSITION HAVING AN ENHANCED DRUG-LOADING CAPACITY AND SUSTAINED RELEASE

(57) Abstract: The present invention relates to a micelle drug composition having an enhanced drug-loading capacity and improved sustained-release characteristics. The composition comprises an amphiphilic block copolymer wherein at least one hydrophilic blocks and at least one hydrophobic blocks form shell and core, respectively, said hydrophobic block comprises 1.1 to 30 functional groups selected from the group consisting of carboxyl, amine, hydroxyl, amide, thiol and sulfonic acid groups, in a hydrophobic block chain of the copolymer.



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**BLOCK COPOLYMER MICELLE COMPOSITION
HAVING AN ENHANCED DRUG-LOADING CAPACITY AND
SUSTAINED RELEASE**

5 **Field of the Invention**

The present invention relates to a micelle drug composition having an enhanced drug-loading capacity and improved sustained drug-release characteristics.

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Background of the Invention

Amphiphilic block copolymers that can form a core-shell type micelle in an aqueous medium have been used for delivering hydrophobic drugs such as anti-cancer drugs, adriamycin and paclitaxel, the drug being loaded in the hydrophobic core and the hydrophilic shell enhancing the solubilization of the micelle.

Such a micelle having a size of not more than 200nm and a polyethyleneoxide hydrophilic shell is neither easily destroyed by the reticuloendothelial or mononuclear phagocyte system nor excreted through kidney, and therefore, circulates in a living body for a long period of time, accumulating at the blood vessel around tumors where the transfer of materials is much enhanced and more selective than that around normal cells.

The hydrophobic block of such amphiphilic block copolymers may be divided into two groups, i.e., (i) a hydrophobic block having no functional group, e.g. polylactide, polycaprolactone, poly(lactide-glycolide), poly(β -benzyl L-aspartate), as way disclosed in Korean Patent Publication Nos. 1999-69033 and 2001-105439, European Patent Publication No. 583055, United States Patent No. 6322805 and Japanese Patent Publication No. 1994-206815, and (ii) a hydrophobic block having a plurality of functional groups, e.g.,

poly(β -substituted aspartate), poly(γ -substituted glutamate), poly(L-leucine), described in European Patent Publication No. 583955. In case the hydrophobic block has no functional group, the drug loading capacity of the hydrophobic core is limited, whereas when contains too much functional groups, for example, 300 or more per hydrophobic block, the amphiphilic nature of the copolymer is lost and dissolves in an aqueous medium and cannot form a micelle. Therefore, the step of chemically bonding a hydrophobic drug to such copolymer has been performed to prepare a delivery composition.

Accordingly, in order to solve this problem and increase the drug loading capacity and sustained-release characteristics of micelle drug composition, there has been a need to develop amphiphilic block copolymeric micelles containing a small quantity of functional groups in a hydrophobic block.

Summary of the Invention

Accordingly, it is a primary object of the present invention to provide a micelle composition for drug delivery having an enhanced drug-loading capacity and sustained-release characteristics.

And it is another object of the present invention to provide a method of preparing such micelle composition, characterized by employing a functional monomer.

Further, it is a further object of the present invention to provide a pharmaceutical composition containing a hydrophobic drug in the hydrophobic core of the micelle composition.

Detailed Description of the Invention

The amphiphilic block copolymer of the present invention comprises one or more of hydrophilic blocks(A) and hydrophobic blocks(B), which

forms a micelle in an aqueous medium, the hydrophilic block(A) and the hydrophobic block(B) forming a shell and a core, respectively. A hydrophobic drug becomes water-soluble when the drug is introduced into the hydrophobic core of such micelle. The hydrophobic block(B) of the present invention carries 1.1 to 30 functional groups, preferably 2 to 30 functional groups, selected from the group consisting of carboxyl, amine, hydroxyl, amide, thiol and sulfonic acid groups which enhance the core's affinity to the drug. Preferably, the amount of the amphiphilic block copolymer having such functional groups is in the range of 0.1 to 10 % by weight, based on the total weight of the micelle composition.

The hydrophilic block of the amphiphilic block copolymer has a molecular weight of preferably 100 to 30,000 Da, more preferably, 1,000 to 12,000 Da. The hydrophilic block of the copolymer may be a poly(alkylene oxide) or monoalkoxy poly(ethylene oxide) block, preferably, poly(ethylene oxide) or methoxy poly(ethylene oxide) block.

The hydrophobic block of the amphiphilic block copolymer is preferably biodegradable and biocompatible, and the molecular weight of the hydrophobic block is preferably from 200 to 30,000 Da, more preferably, from 1,000 to 15,000 Da. The hydrophobic block may be a polylactide, polycaprolactone, polyglycolide, copolymer of lactide and glycolide, polyorthoester, polyanhydride, polyphosphazine, poly amino acid, a mixture thereof, or a derivative thereof, preferably, a polylactide or a copolymer of lactide and glycolide.

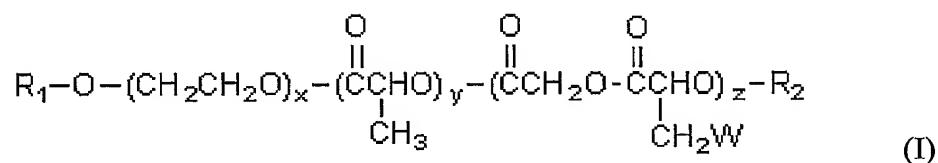
The functional group may be a carboxyl, amine, hydroxyl, amide, thiol or sulfonic acid group. An optimal number of the functional group introduced to the hydrophobic block is 1.1 to 30, which enhances the micelle core's interaction with an essentially water-insoluble drug while maintaining a micellar form in an aqueous medium. Further, such affinity of the drug to the hydrophobic core brings out a desirable sustained-release characteristics of the drug.

Further, the amount of functional groups introduced controls the

degradation rate of the micelle of the present invention. Preferably, the present invention employs a poly(ethylene oxide) as the hydrophilic block, and a polylactide or polycaprolactone as the hydrophilic block, which are nontoxic and have desired biodegradability and biocompatibility.

5 The amphiphilic block polymer of the present invention may be a diblock polymer of the hydrophilic block(A)-hydrophobic block(B) type, or a triblock polymer of the hydrophobic block(B)-hydrophilic block(A)-hydrophobic block(B) or hydrophilic block(A)-hydrophobic block(B)-hydrophilic block(A) copolymer type.

10 As one embodiment of the present invention, the amphiphilic block of formula (I) comprises a hydrophobic block containing a carefully controlled amount of functional groups:



wherein R_1 is H, C_{1-4} alkyl or C_{1-4} acyl;

R_2 is H, C_{1-9} alkyl, aryl or C_{1-9} arylalkyl;

20 x is a number ranging from 10 to 400;

y is a number ranging from 10 to 300;

z is a number ranging from 1.1 to 30; and

W is selected from the group consisting of carboxyl, amine, hydroxyl, amide, thiol and sulfonic acid groups.

25 Herein, x , y or z represent the average number of repeating units of the polymer.

Preferably, the amphiphilic block of formula (I) comprises a hydrophobic block wherein W is a carboxyl group. Preferably, z is the number ranging from 2 to 30. The amphiphilic block of formula (I) comprises a
30 hydrophobic block wherein a ratio z/y preferably ranges from 0.015 to 2, more preferably from 0.02 to 1.5.

The amphiphilic block copolymer of the present invention may be prepared by introducing a controlled amount of functional groups into the hydrophobic block(B) to enhance the core's affinity to a hydrophobic drug.

As one embodiment of the present invention, the amphiphilic block
5 copolymer of formula (I) is prepared as follows:

In the presence of a polyethyleneoxide or monomethoxypolyethyleneoxide, a heterocyclic ester of D,L-lactide is reacted with 3-((bezyloxycarbonyl)methyl)-1,4-dioxane-2,5-dione (BMD, a functional monomer), to obtain an amphiphilic block copolymer, the hydrophobic block
10 thereof comprising benzyl groups, followed by hydro-debenzylation under hydrogen in the presence of a catalyst to obtain an amphiphilic block copolymer comprising carboxyl groups (see International Journal of Biological Macromolecules, 1999, 25, 265).

The functional monomer, 3-((bezyloxycarbonyl)methyl)-1,4-dioxane-
15 2,5-dione (BMD), may be prepared by benzylation of the carboxyl group of aspartic acid in the presence of an acid catalyst and then replacing the amine group with a hydroxyl group. Then, the resultant is bromoacetylated in the presence of a base catalyst to obtain the cyclic structure of BMD (see Macromolecules, 1988, 21, 3338).

20 In accordance with one aspect of the present invention, there is provided a pharmaceutical micellar composition having a core-shell structure, the hydrophobic core of the micelle being designed to load a hydrophobic drug to a higher capacity.

The micellar composition and a drug are dissolved in an organic solvent,
25 and then, the organic solvent is replaced with water, e.g., by dialysis, to obtain an aqueous micelle solution containing the drug. Then, the solution is lyophilized, sterilized and sealed to obtain a pharmaceutical micelle composition containing the drug.

The drug may be present in an amount ranging from 0.1 to 5% by
30 weight based on the total weight of the pharmaceutical composition. A drug

having a solubility of not more than 10mg/ml may be employed. The drug may be an anti-cancer drug, antiinflammation, sex hormone, steroid, anti-hypertensive drug or anti-emesis drug. Preferably, the drug may be paclitaxel, camptothecin, biphenyl dimethyl dicarboxylate, pipsulfan, danazole, taxotere, 5 adriamycin, indomethacin, etoposide, itraconazole, nystatin, hemoglobin or omeprazole.

One embodiment of the medicinal composition of the present invention can be prepared as follows:

10 10 to 500mg of the amphiphilic block copolymer of formula I and 2 to 200mg of a drug, e.g. paclitaxel, adriamycin or indomethacin, are dissolved in 2 to 50ml of an organic solvent, e.g. tetrahydrofuran or dimethylformamide, and 10 to 100ml of distilled water is added thereto. Then, the mixture is stirred for 12 to 36 hours and dialyzed to obtain an aqueous micelle solution containing the drug in the hydrophobic core of the micelle. The aqueous micelle solution 15 may be lyophilized, sterilized and sealed to obtain a pharmaceutical composition for injection.

The micelle composition may be administrated orally or parenterally, for example by injection, for example at a drug concentration of 0.01 to 5mg/ml.

20 The micelle composition of the present invention has a markedly increased drug loading capacity, and sustained-drug release characteristics.

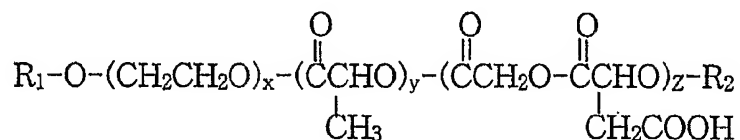
The present invention is further described in the following Examples which are given only for the purpose of illustration, and are not intended to limit the scope of the invention.

25 Preparation of the amphiphilic block copolymers

Preparation Example 1

30 A mixture of 4.0g of methoxy poly(ethylene oxide) (M.W.=5000), 5.7g of D,L-lactide recrystallized from ethyl acetate, 0.3g of 3-

{(bezyloxycarbonyl)methyl}-1,4-dioxane-2,5-dione (BMD, a functional monomer), and 40mg of stannous octoate (a catalyst) was placed in a round-bottomed flask and evacuated for 30 min. to achieve a pressure of 0.001 mmHg. Then, the mixture was allowed to polymerize at 168°C for 2 hours to obtain a diblock copolymer of poly(ethylene oxide-b-lactide), the benzyl groups being introduced into the polylactide block. 4g of the resultant block copolymer was dissolved in 125ml of dioxane in an Erlenmeyer flask, and 1g of a Pt/C catalyst was added thereto. The flask was filled with hydrogen, and then the mixture was allowed to undergo hydro-debenzylation at room temperature, to obtain a diblock copolymer of poly(ethylene oxide-b-lactide), having carboxyl groups introduced into the polylactide block. Nuclear magnetic resonance(NMR) spectroscopy was performed to determine the values of x, y and z from the intensity of each peak of NMR, respectively. The structure of the block copolymer is shown below:



wherein R_1 is CH_3 ; R_2 is H; $x=113$; $y=55.7$; $z=1.34$; and $z/y=0.0241$.

Preparation Example 2

A poly(ethylene oxide-b-lactide) diblock copolymer was prepared by repeating the procedure of Preparation Example 1, except for employing 4.0g of methoxy poly(ethylene oxide)(M.W.=5000), 5.4g of D,L-lactide recrystallized from ethyl acetate, and 0.6g of BMD. The structure of the block copolymer is the same as a preparation Example 1, except for $x=113$; $y=49.4$; $z=2.78$; and $z/y=0.0563$.

Preparation Example 3

A poly(ethylene oxide-b-lactide) diblock copolymer was prepared by repeating the procedure of Preparation Example 1, except for employing 4.0g of methoxy poly(ethylene oxide)(M.W.=5000), 5.1g of D,L-lactide recrystallized from ethyl acetate, and 0.9g of BMD. The structure of the block copolymer is the same as a preparation Example 1, except for $x = 113$; $y = 38.2$; $z = 3.74$; and $z/y = 0.0979$.

Preparation Example 4

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A poly(ethylene oxide-b-lactide) diblock copolymer was prepared by repeating the procedure of Preparation Example 1, except for employing 4.0g of methoxy poly(ethylene oxide)(M.W.=5000), 4.0g of D,L-lactide recrystallized from ethyl acetate, and 2.0g of BMD. The structure of the block copolymer is the same as a preparation Example 1, except for $x = 113$; $y = 33.3$; $z = 11.5$; and $z/y = 0.345$.

Preparation Example 5

20

A poly(ethylene oxide-b-lactide) diblock copolymer was prepared by repeating the procedure of Preparation Example 1, except for employing 4.0g of methoxy poly(ethylene oxide)(M.W.=5000), 2.0g of D,L-lactide recrystallized from ethyl acetate, and 4.0g of BMD as the functional monomer. The structure of the block copolymer is the same as a preparation Example 1, except for $x = 113$; $y = 16.7$; $z = 23.0$; and $z/y = 1.38$.

Comparative Preparation Example 1

A poly(ethyleneoxide-b-lactide) diblock copolymer was prepared by repeating the procedure of Preparation Example 1, except for employing 4.0g of

30

methoxy poly(ethylene oxide)(M.W.=5000) and 6.0g of D,L-lactide recrystallized from ethyl acetate, without adding BMD. The structure of the block copolymer is the same as a preparation Example 1, except for $x=113$; $y=56.1$; $z=0$; and $z/y=0$

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Comparative Preparation Example 2

A poly(ethylene oxide-b-lactide) diblock copolymer was prepared by repeating the procedure of Preparation Example 1, except for employing 4.0g of methoxy poly(ethylene oxide)(M.W.=5000) and 6.0g of BMD, without adding D,L-lactide. The structure of the block copolymer is the same as a preparation Example 1, except for $x=113$; $y=0$; and $z=30.3$.

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Physicochemical Properties of the diblock copolymers

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Physicochemical properties of the amphiphilic copolymers prepared in Preparation Examples 1 to 5 and Comparative Examples 1 and 2 were evaluated. Nuclear magnetic resonance spectroscopy and gel permeation chromatography were used to determine the poly(ethylene oxide) (PEO)/polylactide (PLA) weight ratio and the molecular weight, respectively (see Table 1).

20

Table 1.

	y	z	z/y	Weight ratio (wt%) (PEO/PLA)	M.W.	M.W. Distribution (PDI)
Preparation Example 1	55.7	1.34	0.0241	54.1/45.9	10000	1.14
Preparation Example 2	49.4	2.78	0.0563	55.3/44.7	9010	1.14
Preparation Example 3	38.2	3.74	0.0979	59.5/40.5	8480	1.14
Preparation Example 4	33.3	11.5	0.345	53.2/46.8	10500	1.13

Preparation Example 5	16.7	23.0	1.38	49.0/51.0	10200	1.13
Comparative Preparation Example 1	56.1	0	0	55.3/44.7	10500	1.13
Comparative Preparation Example 2	0	30.3	-	48.7/51.3	10700	1.14

Preparation of the medicinal agent compositions

Examples 1 to 5

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100mg of each copolymer prepared in Preparation Examples 1 to 5, and 50mg of paclitaxel were dissolved in 10ml of dimethylformamide. Then, 10ml of distilled water was added thereto and the mixture was stirred for 24 hours. The resultant mixture was put into a dialysis bag and placed in distilled water for 24 hours to obtain a pharmaceutical composition containing paclitaxel.

Comparative Examples 1 and 2

Pharmaceutical compositions containing paclitaxel were prepared by using the copolymers prepared in Comparative Preparation Examples 1 and 2, respectively, by the same method of Example 1.

Physical properties of the medicinal agent compositions

The drug release rate of each of the compositions prepared in Examples 1 to 5 and Comparative Examples 1 and 2 was measured according to the procedure described in the 2nd volume of Korea Pharmacopeia.

Each micelle containing paclitaxel was homogenously dissolved in 10ml of a dissolution solution(phosphate buffer, pH 7.4), and then the resultant

solution was dialyzed by using a dialysis membrane(molecular weight cutoff, MWCO=8,000). Every hour, 1ml of the drug solution released through the membrane was taken and 1ml of the phosphate buffer was added thereto. Then, the resultant solution was diluted with 2ml of acetonitrile, and quantified by HPLC to determine the drug release rate.

Table 2 shows the micelle diameter, the saturation drug content, the drug release time and the degradation time of the micelle containing paclitaxel. The micelle diameter and the saturation drug content were measured by dynamic light scattering and UV spectrometer, respectively. The drug release time is defined by the time required for releasing 50% of the drug.

Table 2.

	Micelle diameter (nm)	Saturation drug content (wt%)	Drug release time (hr)	Degradation time of the micelle (day)
Example 1	30.0	8.0	21	10
Example 2	28.0	13.7	40	7
Example 3	34.8	14.9	52	6
Example 4	31.3	16.9	59	5
Example 5	28.5	16.8	60	4
Comparative Example 1	42.8	3.8	8	20
Comparative Example 2	-	-	-	-

As can be seen from Tables 1 and 2, the micelles of Examples 1 to 5 have a diameter of about 30 nm, which is appropriate for an injectable drug delivery system.

Each of the compositions of Examples 1 to 5 contained a higher amount of the drug in the hydrophobic core than that of Comparative Example 1. For example, the saturation drug content of the composition of Example 3 ($z = 3.74$,

$z/y = 0.0979$) was approximately 4-fold higher than that of Comparative Example 1 ($z = 0$).

With more carboxyl groups introduced into the hydrophobic block, the drug release time becomes longer. Therefore, by controlling the amount of carboxyl group introduced, one can adjust the sustained-release characteristics of the composition. Further, with increasing the number of carboxyl groups introduced, the micelle degradation time becomes shorter. Accordingly, a micelle composition having more carboxyl groups will rapidly degrade after releasing the drug.

However, if the block copolymer contained too much carboxyl groups ($z > 30$), it fails to form a micelle (see Comparative Example 2 of Table 2), and thus, such copolymer is not suitable for drug delivery system.

It can be seen from the above results, when from 1.1 to 30 carboxyl groups are introduced into the hydrophobic block of the amphiphilic copolymer, the micelle therefrom can carry a large amount of a hydrophobic drug, and exhibit sustained-release characteristics.

While the embodiments of the subject invention have been described and illustrated, it is obvious that various changes and modifications can be made therein without departing from the spirit of the present invention which should be limited only by the scope of the appended claims.

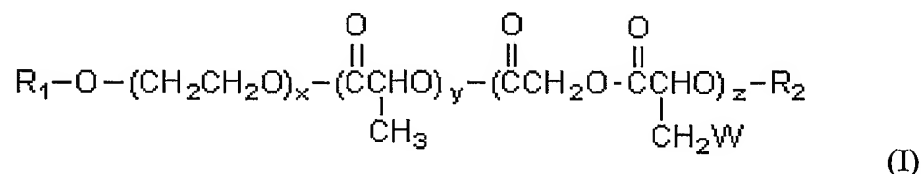
What is claimed is:

1. A micelle composition for drug delivery system comprising an amphiphilic block copolymer having at least one hydrophilic blocks(A) and at least one hydrophobic blocks(B), the hydrophobic block carrying 1.1 to 30 functional groups selected from the group consisting of carboxyl, amine, hydroxyl, amide, thiol and sulfonic acid groups, in a hydrophobic block chain of the copolymer.
2. The composition of claim 1, wherein the amphiphilic block copolymer is present in an amount ranging from 0.1 to 10 % by weight, based on a total weight of the micelle composition.
3. The composition of claim 1, wherein a molecular weight of the hydrophilic block is 100 to 30,000 Da.
4. The composition of claim 3, wherein the hydrophilic block(A) is polyethyleneoxide or methoxypolyethyleneoxide.
5. The composition of claim 1, wherein a molecular weight of the hydrophobic block(B) is 200 to 30,000 Da.
6. The composition of claim 1, wherein the amphiphilic block copolymer is a diblock polymer of the hydrophilic block(A)-hydrophobic block(B) type, or a triblock polymer of the hydrophobic block(B)-hydrophilic block(A)-hydrophobic block(B) or hydrophilic block(A)-hydrophobic block(B)-hydrophilic block(A) type.
7. The composition of claim 1, wherein the hydrophobic block is selected from the group consisting of polylactide, polycaprolactone, polyglycolide, a copolymer of lactide and glycolide, polyorthoester, polyanhydride,

polyphosphazine, poly amino acid, a mixture thereof, and a derivative thereof.

8. The composition of claim 1, wherein the amphiphilic block copolymer is represented by formula (I):

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wherein R_1 is H, C_{1-4} alkyl or C_{1-4} acyl;

R_2 is H, C_{1-9} alkyl, aryl or C_{1-9} arylalkyl;

x is a number ranging from 10 to 400;

y is a number ranging from 10 to 300;

15

z is a number ranging from 1.1 to 30; and

W is selected from the group consisting of carboxyl, amine, hydroxyl, amide, thiol and sulfonic acid groups.

9. The composition of claim 8, wherein W is a carboxyl group.

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10. The composition of claim 8, wherein a ratio z/y ranges from 0.015 to 2.

11. The composition of claim 10, wherein the ratio z/y ranges from 0.02 to 1.5.

25

12. A pharmaceutical composition comprising a hydrophobic drug introduced in the hydrophobic block(B) of the micelle composition according to any one of claims 1 to 11.

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13. The composition of claim 12, wherein the drug is selected from the group consisting of paclitaxel, camptothecin, biphenyl dimethyl dicarboxylate, piposulfan, danazole, taxotere, adriamycin, indomethacin, etoposide,

itraconazole, nystatin, hemoglobin and omeprazole.

14. The composition of claim 12, wherein the drug is present in an amount ranging from 0.1 to 5% by weight, based on the total weight of the micelle
5 composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR03/01065

A. CLASSIFICATION OF SUBJECT MATTER**IPC7 A61K 9/127**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
KOREAN PATENTS AND APPLICATIONS FOR INVENTIONS SINCE 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS(STN), SCISEARCH(STN), PASCAL(STN), COMPENDEX(STN), WPI, USPATFULL, JAPIO

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	WO 03/033592 A1 (SAMYANG CORP.) 24 APRIL 2003 see the whole document	1-7, 12-14
Y	WO 01/87345 A1 (SAMYANG CORP.) 22 NOVEMBER 2001 see the whole document	1-7, 12-14
A	EP 583955 A2 (RESEARCH DEVELOPMENT CORP. OF JAPAN) 23 FEBRUARY 1994 see the whole document	1

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier application or patent but published on or after the international filing date
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 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
 "&" document member of the same patent family

Date of the actual completion of the international search

22 AUGUST 2003 (22.08.2003)

Date of mailing of the international search report

25 AUGUST 2003 (25.08.2003)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR03/01065

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
W003033592A1	24.04.2003	NONE	
W00187345A1	22.11.2001	EP1282447A1 CN1429120T CA2408716AA AU0162756A5	12.02.2003 09.07.2003 22.11.2001 26.11.2001
EP583955A2	23.02.1994	AU4452393A AU668967B2 CA2104045A1 DE69327490D1 JP6107565A KR9609407B1 US5449513A	10.03.1994 23.05.1996 15.02.1994 10.02.2000 19.04.1994 19.07.1996 12.09.1995